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Resistance, Susceptibility, and Immunity to *Eimeria tenella* in Major Histocompatibility *(B)* Complex Congenic Lines

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ABSTRACT The major histocompatibility (*B*) complex influence on resistance, susceptibility, and immunity to *Eimeria tenella* was examined in UCD *B* complex congenic chicken lines. In Experiment 1, 6-wk-old chicks from 12 UCD congenic lines were weighed and assigned to either challenge or control groups. The challenge group received a dose of 10,000 *E. tenella* oocysts. Response to challenge was evaluated by body weight gain and cecal lesion scores. Cecal lesion scores in B^3B^3 chickens were significantly lower than those of all other genotypes. Genotype B^2B^2 had the highest lesion scores, which were significantly different from the lesion scores calculated for B^3B^3, $B^{18}B^{18}$, and $B^{21}B^{21}$ chickens but were not significantly different from $B^{14}B^{14}$, $B^{15}B^{15}$, $B^{17}B^{17}$, $B^{19}B^{19}$, $B^{24}B^{24}$, B^CB^C, B^IB^I, and B^QB^Q genotypes. The $B^{21}B^{21}$ chickens had significantly lower lesion scores than B^2B^2, $B^{14}B^{14}$, and B^CB^C chickens. No other significant lesion score differences were found among the remaining lines. The highest weight gain found in $B^{19}B^{19}$ chickens was significantly different from that of B^3B^3, $B^{14}B^{14}$, $B^{15}B^{15}$, $B^{17}B^{17}$, $B^{18}B^{18}$, $B^{24}B^{24}$, and B^CB^C chickens. The $B^{15}B^{15}$ chickens had the lowest weight gain, which was significantly different from that of B^2B^2, $B^{19}B^{19}$, $B^{21}B^{21}$, $B^{24}B^{24}$, B^IB^I, and B^QB^Q chickens.

Experiment 2 tested the immune response to *E. tenella* after low dose oocyst immunization. Chicks from 10 UCD 003 congenic lines were divided into three groups: control, challenge, and immune. At 5 wk of age, the immune group was immunized with 500 *E. tenella* oocysts for 5 consecutive d. Fourteen days after the last immunization all chicks were weighed, and 10,000 *E. tenella* oocysts were administered to the challenge and immune groups. Significant lesion score differences existed among all three treatments: control (0), immune (2.14 ± 0.1); challenge (3.13 ± 0.1). Among immune birds, B^3B^3 and B^QB^Q chickens had significantly lower lesion scores than $B^{19}B^{19}$, $B^{24}B^{24}$, $B^{14}B^{14}$, and B^2B^2 chickens. Neither $B^{19}B^{19}$ nor $B^{24}B^{24}$ chickens were well-protected, as indicated by their higher lesion scores. No significant differences in weight gain were found in immune birds.

The *B* complex affected resistance and susceptibility as well as the immune response to *E. tenella*. Cecal lesion scores following challenge in naive birds or after immunization were influenced by the *B* complex, whereas weight gain was affected in naive birds only. These effects may be manifested through differences in immune competence at the time of challenge or immunization, the amount of parasite antigen production, or the threshold doses for effective immunization.

(*Key words*: major histocompatibility complex, parasite immunity)

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INTRODUCTION

Coccidiosis, a disease caused by obligate intracellular protozoan parasites of the genus *Eimeria*, constitutes a significant economic impact in poultry. Lower weight gain, reduced feed efficiency, mortality, and prophylactic medication are important cost factors (Danforth and Augustine, 1985). Anticoccidial compounds provide control despite increased drug resistance and decreased development of new medications. Host resistance or increased immune response represent potential alternative control methods.

Genes of the MHC (*B* complex) influence the response to many diseases in the chicken. Diseases caused by oncogenic and nononcogenic viruses, bacteria, and parasites are affected by the host MHC (Dietert *et al.*, 1991). Briles and coworkers (1977) demonstrated that the B^{21} haplotype of the chicken MHC is responsible for strong resistance to Marek's disease, whereas B^{19} is associated with a high degree of susceptibility. Collins and coworkers (1977) determined that B^2B^2 chickens regressed Rous sarcoma virus-induced tumors and B^5B^5 birds progressed these tumors. the B^5 haplotype provided a more effective response against *Eimeria tenella* than did B^2 (Clare *et al.*, 1985). These results are opposite to that observed for Marek's disease, lymphoid leukosis, and Rous sarcomas, in which the B^2 haplotype exhibited superior responses (Plachy *et al.*, 1992).

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TABLE 1. Major histocompatibility (*B*) complex congenic lines of chickens obtained from the University of California-Davis (Abplanalp, 1992)

Line	*B* Haplotype[1,2]	Source line
1004	B^{17}	UCD 003 Inbred full-sib (1956) White Leghorn
1104	B^{O}	UCD 500 Ceylonese Jungle Fowl × Red Jungle Fowl
253	B^{18}	UCD 002 Inbred White Leghorn
254	B^{15}	UCD 007 Inbred White Leghorn
312	B^{24}	UCD 200 NH Inbred
313	B^{3}	UCD 071 Inbred White Leghorn
316	B^{14}	UCD 400 NH Wisconsin Inbred
330	B^{21}	UCD 100 Inbred Australorp
331	B^{2}	Hy-Line Dwarf White Leghorn
333	B^{J}	UCD 001 Inbred Red Jungle Fowl
335	B^{19}	UCD 159 Mount Hope Commercial Richardson
336	B^{Q}	UCD 001 Inbred Red Jungle Fowl
342	B^{C}	UCD 500 Ceylonese Jungle Fowl × Red Jungle Fowl

[1]Haplotypes with numerical superscripts are in accordance with international nomenclature as described by Briles and Briles (1982).

[2]Haplotypes with as yet undefined status are designated with capital superscripts.

Resistance to coccidiosis is very complex involving several host factors, which include age, immune competence, and genetic composition (Lillehoj, 1988). Chickens having increased resistance or susceptibility to coccidiosis have been produced through selective breeding (Edgar *et al.*, 1951; Champion, 1954; Rosenberg *et al.*, 1954; Johnson and Edgar, 1982). The overall mechanisms responsible for the differences in resistance to infection among different lines involve both MHC and non-MHC genes (Lillehoj *et al.*, 1986; Lillehoj, 1988; Clare and Danforth, 1989; Bumstead and Millard, 1992).

Development of congenic lines having a common highly inbred genetic background and differing in their MHC (Abplanalp, 1992) has created an opportunity to compare the degree of disease resistance conferred by specific *B* complex haplotypes. In the present study, resistance, susceptibility, and immunity to *E. tenella* were tested in UCD 003 *B* complex congenic lines. The first experiment examined the genetic differences between resistance and susceptibility. A second study investigated the congenic lines' response to immunization with small doses of oocysts prior to challenge.

MATERIALS AND METHODS

Stocks

The *B* congenic lines used in this study are shown in Table 1. These lines were produced by crossing *B* haplotypes from different sources into the genetic background of Line UCD 003 ($B^{17}B^{17}$) followed by five backcrosses (Abplanalp, 1992). Heterozygotes were then mated *inter se* to produce progeny that were homozygous for different *B* haplotypes. Fertile eggs were shipped from the University of California-Davis to the University of New Hampshire Poultry Research Farm, where they were incubated and hatched. Chicks were vaccinated against Marek's disease and Newcastle-bronchitis at 1 and 10 d, respectively. Birds were housed in isolation, free from any possible coccidial exposure, in wire floor cages with free access to antibiotic-free feed and water.

Coccidial Cultures

Fresh cultures of the Lilly 65 strain of *E. tenella* oocysts were obtained from a stock culture held at the University of New Hampshire. The stock culture was propagated in susceptible 3- to 5-wk-old chickens inoculated with 6 to 7 × 10^4 sporulated oocysts per bird. After 7 d, the chickens were euthanatized and oocysts harvested directly from the cecal pouches. Following peptic digestion (Rikimaru *et al.*, 1961), sporulation of the oocysts was enhanced by bubbling with air in 0.5% potassium dichromate at room temperature, then sterilized using a 50% chlorine bleach solution (Wagenbach and Burns, 1969). The culture was held up to 3 mo at 4 C until used.

Criteria of Evaluation

Cecal lesion scores were used to measure severity of infection in Experiment 1 and degree of immune response in Experiment 2. Scoring followed the procedure of Johnson and Reid (1970) where 0 = no gross lesions; 1 = very few scattered petechiae on the cecal wall; no thickening of the cecal walls; normal cecal contents; 2 = lesions more numerous with noticeable blood in the cecal contents; cecal wall is somewhat thickened; normal cecal contents present; 3 = large amounts of blood or cecal cores present; cecal walls greatly thickened; little, if any, fecal contents in the ceca; and 4 = cecal wall greatly distended with blood or large caseous cores, fecal debris lacking or included in cores. Dead birds were scored as 4.

Birds were weighed on Day 1 prior to inoculation with oocysts, and again on Day 6. Weight gain was calculated by subtracting the initial weight from the weight on Day 6. Mortality after inoculation was also determined for all groups.

Experiment 1. Susceptibility

Chicks from 12 *B* complex congenic lines having genotypes: B^2B^2, B^3B^3, $B^{14}B^{14}$, $B^{15}B^{15}$, $B^{17}B^{17}$, $B^{18}B^{18}$, $B^{19}B^{19}$, $B^{21}B^{21}$, $B^{24}B^{24}$, B^CB^C, B^IB^I, B^QB^Q, were used. At 6 wk of age, all chicks were weighed and assigned to either challenge or control groups. The control group received no inoculation. The challenge group received a dose of 10,000 Lilly 65 strain *E. tenella* oocysts. Inocula were counted using a hemocytometer and were administered *per os* to the crop using an inoculation tube and syringe. Each line was represented by four to five chicks in control as well as challenge groups in three hatches constituting a total of 351 individuals. Cecal lesion scores, body weight gain, and mortality were measured 6 d following exposure.

Experiment 2. Immunity

Chicks from 10 of the UCD 003 *B* complex congenic lines having genotypes: B^2B^2, B^3B^3, $B^{14}B^{14}$, $B^{15}B^{15}$, $B^{17}B^{17}$, $B^{19}B^{19}$, $B^{24}B^{24}$, B^CB^C, B^QB^Q, and B^OB^O, were tested in two hatches for immune response to *E. tenella*. Chicks were divided into three groups: control, challenge, and immune. A total of 187 chicks were used with 6 to 9 chicks from each line in each treatment. The control group consisted of a pooled sample of several chicks from each genotype and received no inoculation. At 5 wk of age, the immune group was immunized with 500 *E. tenella* oocysts for 5 consecutive d as described previously (Clare *et al.*, 1986). Fourteen days after the last immunization all chicks were weighed and the challenge and immune groups received a dose of 10,000 *E. tenella* oocysts. The challenge birds were compared to the immune group to demonstrate protection provided by immunization. Cecal lesion scores, body weight gain, and mortality were measured 6 d following challenge as in Experiment 1.

Statistical Analysis

Mean cecal lesion scores and body weight gain were evaluated by analysis of variance. In Experiment 1, the challenge group was analyzed with hatch and line as main effects. Hatch, line, and treatment were the main effects in the analysis of Experiment 2 to determine the efficacy of the immunization regimen. The immune group was analyzed for differences among lines in their response to immunization. Significant means for both experiments were separated by Fisher's protected Least Significant Difference at $P < 0.05$.

RESULTS

Experiment 1 compared resistance and susceptibility among 12 UCD *B* complex congenic lines inoculated with 10,000 *E. tenella* oocysts. The control group received no inoculation and produced no cecal lesions. The mean cecal lesion scores of the challenge group are shown in Figure 1. Lesion scores in B^3B^3 chickens were significantly lower than the scores of every other genotype tested. The $B^{21}B^{21}$ genotype had the next lowest lesion score, which was significantly different from scores of the B^2B^2, $B^{14}B^{14}$, and B^CB^C genotypes. Chickens of the B^2B^2 genotype had the highest cecal lesion scores, which were significantly greater than the lesion scores found in B^3B^3, $B^{18}B^{18}$, and $B^{21}B^{21}$ lines. Lesion scores of B^2B^2 chickens of the genotype were not statistically significant relative to scores of $B^{14}B^{14}$, $B^{15}B^{15}$, $B^{17}B^{17}$, $B^{19}B^{19}$, $B^{24}B^{24}$, B^CB^C, B^IB^I, and B^QB^Q genotypes. Based on lesion scores after primary inoculation, B^3B^3 chickens were more resistant to *E. tenella* than any other line tested. No single line showed increased susceptibility although B^2B^2 chickens were more susceptible than were B^3B^3, $B^{18}B^{18}$, and $B^{21}B^{21}$ chickens.

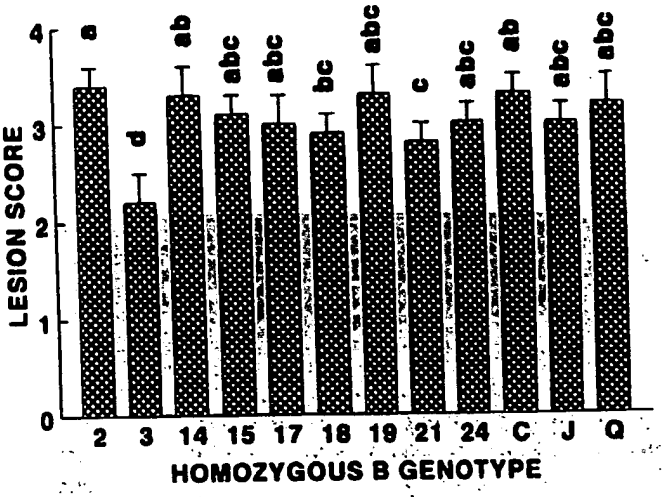

FIGURE 1. Mean cecal lesion scores in UCD *B* complex congenic line chickens 6 d after inoculation with 10,000 *Eimeria tenella* oocysts at 6 wk of age. Bars having no letters in common differ significantly ($P < 0.05$).

Mean weight gains 6 d after 10,000 *E. tenella* oocyst inoculation are shown in Figure 2. Genotype $B^{19}B^{19}$ had

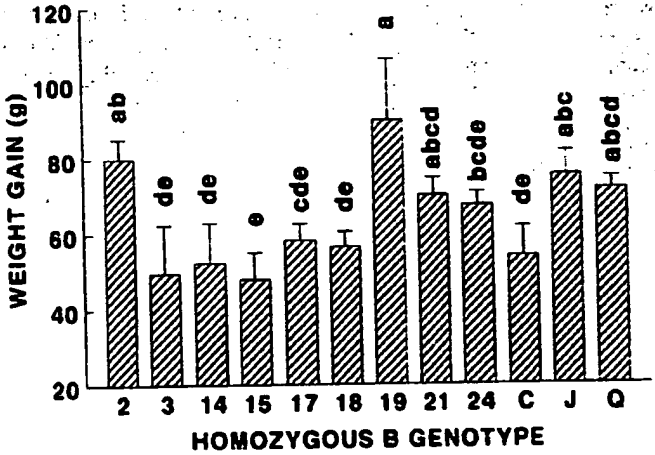

FIGURE 2. Mean weight gain (grams) in UCD *B* complex congenic line chickens 6 d after inoculation with 10,000 *Eimeria tenella* oocysts at 6 wk of age. Bars having no letters in common differ significantly ($P < 0.05$).

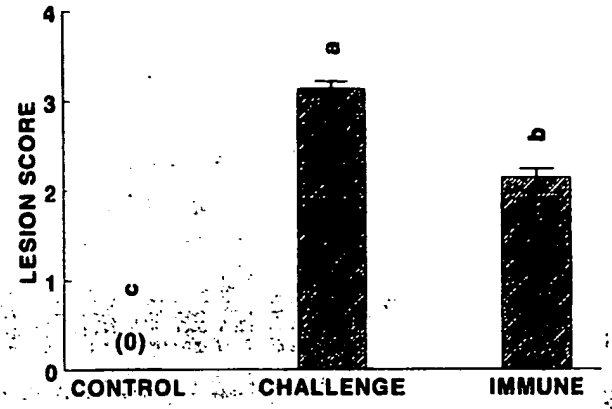

FIGURE 3. Mean cecal lesion scores in control, challenge, and immune UCD *B* complex congenic line chickens. Immune birds were immunized with 500 *Eimeria tenella* oocysts for 5 consecutive d and challenged with 10,000 *E. tenella* oocysts 14 d after the last immunization. Control birds were not exposed. Challenge birds received 10,000 *E. tenella* oocysts only. Each of the three groups represents an average score of all the congenic lines. Bars having no letters in common differ significantly ($P < 0.05$).

the highest weight gain, which was significantly different from B^3B^3, $B^{14}B^{14}$, $B^{15}B^{15}$, $B^{17}B^{17}$, $B^{18}B^{18}$, $B^{24}B^{24}$, and B^CB^C. The lowest weight gain, exhibited by $B^{15}B^{15}$ chickens, was significantly lower than B^2B^2, $B^{19}B^{19}$, $B^{21}B^{21}$, B^IB^I, and B^QB^Q. The B^3B^3 chickens, which had the lowest cecal lesion score, had the second lowest weight gain. The correlation coefficient for lesion score and weight gain was 0.126 indicating little relationship between the two criteria for the 351 chicks in Experiment 1.

In Experiment 2, immunity was evaluated after an immunizing regimen consisting of daily inoculations of 500 *E. tenella* oocysts for 5 d followed by challenge with 10,000 oocysts 14 d after the final immunizing dose. Immunization was successful because the three groups were significantly different from each other (Figure 3). The control group was not exposed to coccidia and had no cecal lesions. The challenge group, which had no exposure to coccidia prior to challenge, had the highest lesions (3.13 ± 0.1), whereas the immune group, which had been previously immunized, had an intermediate value (2.14 ± 0.1).

Among immune birds, B^3B^3 and B^QB^Q chickens had lesion scores, which were significantly lower than those of the $B^{19}B^{19}$, $B^{24}B^{24}$, $B^{14}B^{14}$, and B^2B^2 chickens (Figure 4). Lesion scores found in the $B^{19}B^{19}$ and $B^{24}B^{24}$ chickens were significantly higher than B^3B^3, $B^{15}B^{15}$, B^CB^C, and B^QB^Q chickens, suggesting that the former two genotypes were not well-immunized compared to the latter four genotypes. The B^3B^3 genotype had the lowest numerical lesion scores postimmunization as well as the lowest numerical lesion scores postprimary challenge in Experiment 1. No significant differences in weight gain and no correlation between lesion score and weight gain were found in immune birds (data not shown).

DISCUSSION

In Experiment 1, 12 *B* congenic lines of chickens having the common UCD genetic background were compared for their resistance to coccidial infection. Some *B* complex genotypes were more resistant than others following 10,000 *E. tenella* oocyst challenge. The B^3B^3 and $B^{21}B^{21}$ genotypes were more resistant to *E. tenella* than B^2B^2 chickens, which were more susceptible based on cecal lesion scores. The remaining nine genotypes were not significantly different from each other.

The $B^{19}B^{19}$ chickens had the highest weight gain and the $B^{15}B^{15}$ chickens had the lowest weight gain (Figure 2). There was little relationship between lesion score severity and weight gain in the congenic lines, as detected in other studies (Clare *et al.*, 1985; Martin *et al.*, 1986; Ruff and Bacon, 1989). Genotype $B^{19}B^{19}$ was the most resistant by the weight gain criteria, but these birds had high lesion scores as well. On the other hand, the B^3B^3 chickens, which were most resistant as measured by low lesion scores, also had low weight gain. These results reemphasize the dilemma in choosing a single criterion on which to base resistance or susceptibility (Ruff and Bacon, 1989).

Both criteria, lesion scores and weight gain, reflect certain aspects of the response to the parasite, but neither alone can be relied upon to depict the overall immune competence of the individual. Lesion scores represent the parasite's physical damage to the host's intestines. Variables such as lymphocyte and parasite numbers, which may affect lesion scores, are related to the immune response. Additional variables affect weight gain, such as feed consumption or nutrient processing efficiency during infection. Birds with severe intestinal lesions have gained weight during a coccidial infection,

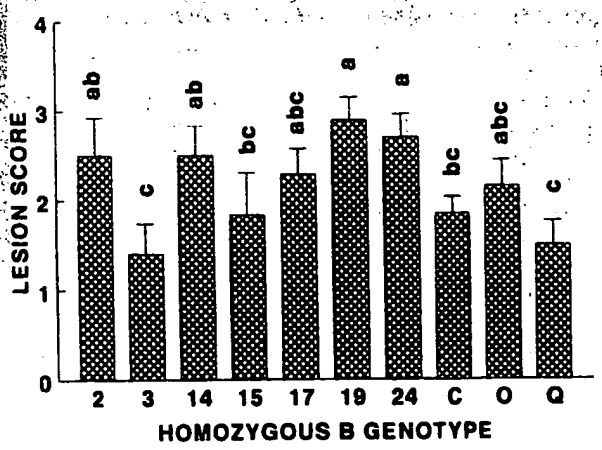

FIGURE 4. Mean cecal lesion scores in UCD *B* complex congenic line chickens immunized with 500 *Eimeria tenella* oocysts for 5 consecutive d and challenged with 10,000 *E. tenella* oocysts 14 d after the last immunization. Bars having no letters in common differ significantly ($P < 0.05$).

and birds showing fewer lesions have gained very little weight.

The immunizing protocol in the Experiment 2 used five consecutive daily doses of 500 *E. tenella* oocysts. Immunization was successful because immunized birds had lower lesion scores than the unimmunized, challenged birds. Differential *B* haplotype effects were seen among the immunized UCD congenic lines. Immunized B^3B^3 and B^QB^Q chickens had lower lesion scores than the $B^{19}B^{19}$, $B^{21}B^{24}$, $B^{14}B^{14}$ and B^2B^2 genotypes. Genotypes $B^{15}B^{15}$, $B^{17}B^{17}$, B^CB^C, and B^OB^O were intermediate in response.

Previous studies revealed significantly greater immunity to *Eimeria* following daily low doses of oocysts compared to the same total oocyst number in a single immunizing dose (Joyner and Norton, 1973; Joyner and Norton, 1976). Clare *et al.* (1986) demonstrated that repeated daily doses of 200 oocysts did not induce detectable immunity, whereas five daily doses of 500 oocysts stimulated protection in progeny segregating for B^2 and B^5 haplotypes. The higher immunizing dose reached or exceeded the threshold to stimulate immunity (Clare *et al.*, 1986). The immunizing threshold may not have been achieved in the current study's poor responding lines.

The current results corroborate previous studies (Clare *et al.*, 1985; Lillehoj *et al.*, 1986; Lillehoj and Ruff, 1987; Ruff and Bacon, 1989) indicating an important role for the *B* complex in response to primary infection and in the development of immunity to *E. tenella*. The poor response exhibited by the B^2B^2 genotype was found by Clare and colleagues (1986) and Ruff and Bacon (1989). Two congenic lines (15.6-2 and 15.7-2) having the B^2 haplotype from different donor lines, both had higher susceptibility to primary *E. tenella* infection based on weight gain, oocyst production and plasma pigment values compared to lines containing the B^5, B^{12}, B^{13}, and B^{19} haplotypes (Ruff and Bacon, 1989). No lesion score differences were observed. These same two B^2B^2 congenic lines also were more susceptible to *Eimeria acervulina* as indicated by weight gain postchallenge.

The B^2B^2 genotype had less protection following repeated low dose immunization than the B^5B^5 chickens (Clare *et al.*, 1985). A genetically engineered *E. tenella* antigen also stimulated less protective immunity in B^2B^2 congenic chickens than in the B^5B^5 line (Clare and Danforth, 1989). On the other hand, Ruff and Bacon (1989) found that congenic lines 15.6-2 and 15.7-2 (B^2B^2) had low immunity to *E. tenella* after a single 100 oocyst immunization but had 84% protection after four 100 oocyst doses. Congenic line 15.15I-5 (B^5B^5) had only 23% protection in the same protocol.

Responses of individual *B* haplotypes may be influenced by non-MHC background genes (Clare *et al.*, 1985; Lillehoj *et al.*, 1986; Lillehoj and Ruff, 1987; Ruff and Bacon, 1989). Congenic lines minimize the background genes influence by placing particular *B* haplotypes on a common genetic background. However, differences in genetic background genes among various chicken lines, alter the context in which particular *B* haplotypes are expressed. Three studies found differential immune responses between B^2 from line 6, and B^5 from line 15 (Clare *et al.*, 1985; Clare and Danforth, 1989; Ruff and Bacon, 1989) in two genetic backgrounds: inbred line 6 in the former two studies and inbred line 15 in the latter study. The B^2B^2 genotype also showed a poor response in the current study, using the UCD 003 background, which supports the low response of the B^2 haplotype. Conversely, successful immunization of the B^2B^2 genotype on the Line 15 background (Ruff and Bacon, 1989) but not in B^2B^2 on the Line 6 background (Clare *et al.*, 1985; Clare and Danforth, 1989) suggests a non-MHC background gene influence.

Mechanisms for protective immunity to chicken coccidiosis are thought to depend on T cells (Giambrone *et al.*, 1980; Lillehoj, 1987; Rose and Long, 1971), with the possibility of a secondary role for antibodies (Rose and Hesketh, 1979; Crane *et al.*, 1986; Clare and Danforth, 1989). Therefore, quantitative differences in T cell numbers may influence the qualitative aspects of cellular immunity. Line FP ($B^{15}B^{21}$) chicks have more splenic T lymphocytes than Line SC (B^2B^2) chicks at 1 d of age. A single primary inoculation stimulated protective immunity at 1 d of age in Line FP whereas Line SC did not develop equivalent immunity until 4 wk of age (Lillehoj, 1988).

Recognition of parasite antigens may differ among particular *B* complex haplotypes. For example, B^2B^2 and $B^{19}B^{19}$ genotypes had high lesion scores after primary inoculation and a poor response to immunization, whereas genotypes $B^{15}B^{15}$ and B^QB^Q also had high lesion scores, but showed good response to immunization. Congenic lines in the present study may also differ in their immune competence at the time of vaccination as influenced by the number of mature T cells or the amount of processed antigen available to stimulate a T cell response. These effects could be related to MHC genes, background genes or a combination of the two.

The amount of antigen to stimulate immunity may fluctuate based on the number of parasites produced at various life-cycle stages. Quist *et al.* (1993) showed that cells from a line selected for a sixfold differential resistance to *E. tenella* had less initial parasite infection and less subsequent asexual stage development than did cells from the susceptible line. These lines differ in their frequencies of particular *Ea-A* and *Ea-E* blood group antigens as well (Johnson and Edgar, 1984). Some haplotypes, which had lower lesion scores after primary inoculation in the current study, may not produce sufficient parasites to stimulate immunity resulting in their lower protection after immunization.

Both *B* complex and background gene effects should be considered in the evaluation of responses to *E. tenella* infection and the acquisition of immunity. The same background genes present in a series of congenic lines may have variable interaction with a spectrum of *B* haplotypes. Likewise, responses of similar *B* complex

haplotypes may differ depending upon the particular genetic background.

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